Letter to the Editor

Acetaminophen to treat fever in intensive care unit patients with likely infection: a response from the author of the HEAT trial

Paul Young[1,2]

[1]Intensive Care Unit, Wellington Hospital, Wellington, New Zealand; [2]Medical Research Institute of New Zealand, Wellington, New Zealand
Correspondence to: Dr. Paul Young. Intensive Care Unit, Wellington Hospital, Riddiford Street, Newtown, Wellington 6021, New Zealand. Email: paul.young@ccdhb.org.nz.

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The HEAT trial was a phase 2b randomized, double-blind, placebo-controlled trial designed to provide preliminary data on the safety and efficacy of using intravenous acetaminophen (paracetamol) to treat fever in intensive care unit (ICU) patients with likely infection (1,2). The trial and its interpretation in the wider context of existing literature on fever control were discussed in commentaries (3,4) and a perspective (5) published in recent issues.

The various interpretations offered are very reasonable; however, some points require clarification. In relation to the proportion of eligible patients enrolled, the recruitment rate in the HEAT trial (6) is similar to that seen in many large-scale multicenter randomized controlled ICU trials and there is no reason to believe that the results are not broadly applicable to ICU patients with fever and likely infection. Study medication was given entirely in accordance with the protocol in 281 out of 347 patients assigned to receive acetaminophen (81%) and 289 out of 344 placebo patients (84%). Protocol deviations that occurred were minor (e.g., missing a dose or giving an extra dose of study medication) and are unlikely to have materially affected the findings. Variations in the administration of study medication are expected in a pragmatic trial and, in this case, they do not diminish the relevance of the study findings because they reflect the idiosyncratic way in which acetaminophen is used to treat fever in clinical practice. Acetaminophen is commonly used as an analgesic and so open-label acetaminophen was allowed in our study protocol once the course of study medication was completed. Use of open label acetaminophen in such circumstances does not undermine the trial findings in relation to the question of whether or not acetaminophen should be used to treat fever. Our decision to enroll patients with a temperature of ≥38 ℃ was based on an inception cohort study (7) showing that among patients with a temperature of ≥38 ℃ who were treated with antimicrobials, acetaminophen was administered between 58% and 70% of the time on each of the first seven days in ICU. We consider it unlikely that our findings would have been different if we had used a threshold of 38.3 ℃ to define fever.

For many clinicians an additional consideration when they are deciding how to apply the HEAT study findings to their practice may be that the HEAT trial did not evaluate whether administering acetaminophen to treat fever made patients feel better or not. We chose not to assess this because we considered that how the patient was feeling would be difficult to assess in our study population due to the frequent use of sedation and mechanical ventilation. Additionally, we considered that competing risks of ICU discharge or death could potentially confound any such assessment. Although, in a recent study of adults with influenza, regular administration of acetaminophen was not associated with improved symptom scores compared to placebo (8), the question of whether using acetaminophen to treat fever makes ICU patients with infections feel better remains unanswered.

Although Ray and Schulman (5) suggest that the evolutionary perspective favors the 'let it ride' approach, the HEAT trial data do not particularly support this approach in ICU patients with likely infection. Indeed, in three high-quality randomized controlled trials (6,9,10) evaluating interventions that reduce body temperature in critically ill patients with infection, point estimates favored the more aggressive temperature control strategy.

One potential explanation for why arguments based on evolutionary biology may not hold true in ICU patients is that without ICU treatment the sickest patients would certainly die. In other words, humans have not evolved to survive illnesses that require organ support in an ICU. ICU treatment allows patients to be supported beyond the limits of normal physiological homeostasis. In essence, if an illness is reversible, patients survive if they can be supported long enough to recover. However, there are limits to supportive care and when these limits are exceeded, progressive multiorgan failure develops and patients often die. Temperature control may reduce metabolic demands and thereby prevent the extended limits of homeostasis offered by supportive ICU therapy being exceeded. While acetaminophen appears to neither improve nor worsen outcomes in ICU patients with fever and likely infection overall (6), it is possible that the adaptive advantages of 'letting fever ride' prevail in patients with lower illness acuity and that treating fever is a better approach in patients requiring high levels of ICU support. We are planning to conduct an individual patient data meta-analysis of existing trials of temperature control to evaluate this hypothesis further in ICU patients with high illness acuity but, ultimately, a large-scale randomized controlled trial is likely to be required to confirm or refute this possibility. For now, we know that while the antipyretic effects of acetaminophen appear to be relatively modest, the medication appears to be well tolerated. Clinicians can be reassured that administration of acetaminophen to ICU patients with fever and likely infection does not appear to be harmful (6). These data provide some reassurance for situations when acetaminophen is used to treat pain in ICU patients with infections but also suggest that administering acetaminophen to treat fever alone in these patients is generally is not necessary.

In my view, the HEAT trial should be considered 'practice-informing' rather than 'practice-changing'. As a phase 2b trial, it was only designed to provide preliminary data; however, it still provides the first high quality evidence of the clinical consequences of using acetaminophen to treat fever in ICU patients with likely infection.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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